



# A Computational Study Of The Treatment For Colorectal Cancer Using *Alangium Salviifolium*

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## Abstract

The marketed medicine for cancer has various side effects, and the minimisation of the side effects using a natural product is rising. In this study, *Alangium salviifolium* was used for its constituents. The alkaloids, namely, Deoxytubulosine and Beta-carboline harmaline, present in plants, have anticancer properties. CADD, a computational-based designing method, was used to understand the alkaloids' anticancer activity. The anticancer properties of the compounds using the NPACT database, and the binding affinity study were carried out with six different receptors using the Auto Dock software, with results visualised in Discovery Studio. These results were evaluated with the standard marketed drug Paclitaxel. For the extra benefits, the compounds were modified with Zinc Oxide. After modification, the results of the molecular docking study using the PyRx software were visualized in Discovery Studio. The pharmacokinetics study using the pkCSM database needs in-vitro validation of Beta-carboline harmaline.

**Keywords:** Cancer, Colorectal, Bioinformatics, treatment

## Introduction

As Prathima Shashi Kumara et al. say, cancer is a collection of diseases described by the uncontrolled multiplication of cells that attack and affect nearby cells. (C, Shashikumara and T, 2019). Colorectal cancer (CRC) is also known as colon cancer or bowel cancer. According to K. Van Der Jeught *et al.*, colon cancer is the third most common cancer influencing both men and women. (Van Der Jeught *et al.*, 2018) 60% of medications currently utilised for cancer treatment have been isolated from regular drugs, and the plant kingdom has been a significant source.

According to E. Solowey *et al.*, vinca alkaloids, Taxus diterpenes, Camptotheca alkaloids, and Podophyllum ligands are the compounds used to treat cancer. (Solowey *et al.*, 2014). The mechanism of the plant-based medication is almost standard, i.e. the induction of apoptosis is shown by P. Aiello *et al.*, (Aiello *et al.*, 2019).

As stated by S. Shravya *et al.*, *Alangium salviifolium* is one of India's most commonly utilized therapeutic plants and is frequently found in Southeast Asia. (Shravya, Vinod, and Sunil, 2017) The plant is also found in Africa, Madagascar, Southern and Eastern Asia, tropical Australia, the New Pacific Sea islands, and New Caledonia. (Shravya, Vinod, and Sunil, 2017).

According to M. Ratra *et al.*, the plant has many medicinal properties, which include Antidiabetic action, Antiulcer action, Antiarthritic action, Antihelmintic action, Antioxidant action, Antimicrobial action, Antifertility action, Analgesic and mitigating action, Diuretic action, Antiepileptic action, Antifungal action, and Hepatoprotective action. (Ratra *et al.*, 2012).

The anticancer activity of the plant is exhibited by the alkaloids Deoxytubulosine and Beta-carboline harmaline, which has been shown by P. Bama. (P. Bama, 2011). The experiments performed by A. Mondal *et al.*, show that the alkaloids belong to the  $\beta$ -carboline-benzo quinolizidine alkaloid, which exhibits activities by inhibiting the DNA topoisomerases and interfering with DNA synthesis (Mondal *et al.*, 2019).

Computer-Aided Drug Design (CADD) is a method that plays a crucial role in designing a drug that is cost-effective and limits the use of animal models for any potential drug candidate. It also helps in designing novel and safe drug candidates for repositioning the marketed drug (Brogi *et al.*, 2020).

## Methodology

Active constituents and the standard drug were retrieved from the PubChem database and DrugBank. The NPACT (Naturally occurring Plant-based Anticancerous Compound-Activity-Target) database has been used to predict active constituents' anticancer properties. The target molecule was retrieved using the RCSB protein Data Bank (PDB) for different target molecules based on the nature of the standard drug and test compounds.

### Prediction of binding sites of a target molecule

The binding site of the target molecule is the region where ligands bind during the biochemical reaction. The CASTp (Computed Atlas of Surface Topography of Proteins) database was used to predict where the binding site is present in a target molecule.

### Binding activity study of the target molecule and active constituents

For the binding affinity study, molecular docking was performed between the target molecule and the active constituents of the plant and the control drug Paclitaxel using AutoDock 4 software (MGL tools), which provides the binding models with its binding affinity and RMSD value.

### Modification of compounds

For the enhancement of the study compound Molinspiration cheminformatics (<https://www.molinspiration.com/>) database that provides the bioactivity of the compounds from which it can be predicted that the proper or improper formation of the compound was used. This database uses the canonical smiles format for the construction of the compound. The compounds were modified by adding the Zinc oxide molecule.

PyRx software provided the binding affinity and RMSD values for the modified compounds' molecular docking.

### Pharmacokinetics prediction of the compound

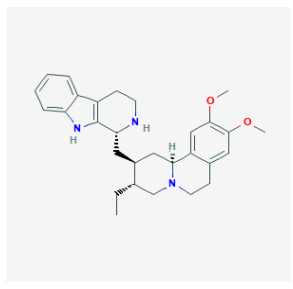
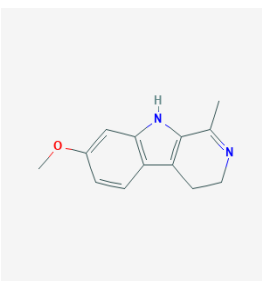
The pharmacokinetics prediction was performed to determine the compound's Absorption, Distribution, Metabolism, Excretion, and Toxicity. The pkCSM tool (<http://biosig.unimelb.edu.au/pkcsm/>) database was used for the prediction.

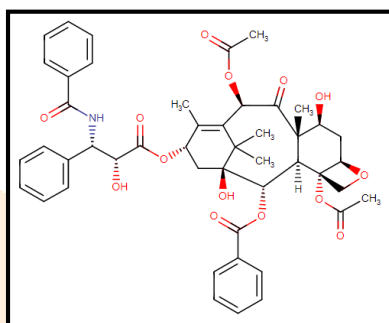
## Results and Discussion

### Retrieval of the active constituents and the standard drug

S. Kim *et al.*, suggested that PubChem is an open repository of chemical substances and their biological activities' information (Kim *et al.*, 2016). Therefore, it was used for the retrieval of active constituents and standard drugs. The active constituents used for the study are Deoxytubulosine and Beta-carboline harmaline. Paclitaxel was considered a standard drug for this study. The canonical Smiles and the structure were retrieved using PubChem. The PubChem ID, Molecular Weight, Molecular Formula, Canonical Smiles, and the structure used in the study are described in Table 1. S. Bundela *et al.*, used PubChem the identification of potential compounds for the treatment of oral cancer (Bundela, Sharma, and Bisen, 2015). DrugBank is an online database that provides information on drugs in the market and is experimentally based, as stated by D. Wishart *et al.* (Wishart *et al.*, 2008). In this study, the standard drug used was paclitaxel. Paclitaxel (DrugBank accession number—DB01229) is used to treat CRC. It is a mitotic inhibitor isolated from the bark of the Pacific Yew tree, which contains entophytic fungi that synthesize paclitaxel. The structure of Paclitaxel is shown in Figure 1.

**Table 1: Details of active constituents.**

Name of compounds	Deoxytubulosine	Beta-carboline Harmaline
PubChem ID	165003	3564
Molecular Formula	C <sub>29</sub> H <sub>37</sub> N <sub>3</sub> O <sub>2</sub>	C <sub>13</sub> H <sub>14</sub> N <sub>2</sub> O
Molecular Weight	459.6 g/mol	214.26 g/mol
Structure		

**Figure 1: Structure of Paclitaxel**

### Anticancer properties prediction of the compounds

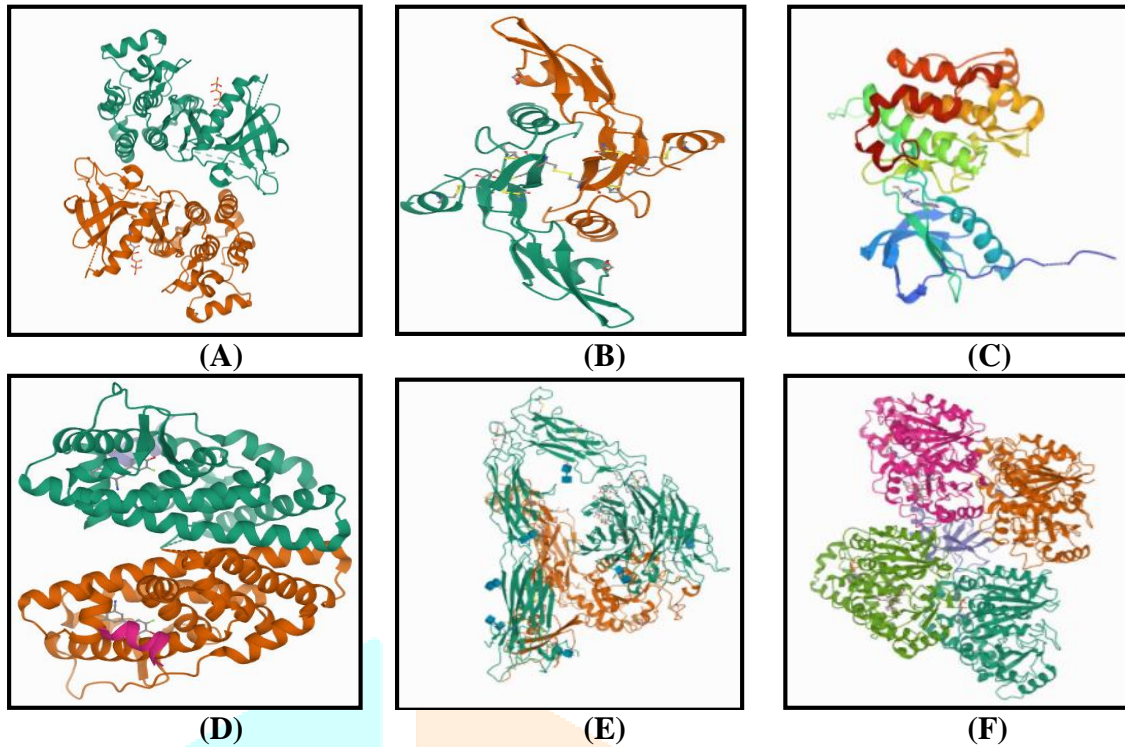
To predict, the NPACT tool was used in this study as given by M. Manga *et al.* (Mangal *et al.*, 2013). According to NPACT, the EC<sub>50</sub> value for Deoxytubulosine is 0.05µg/mL.

In this context, the dosage of Deoxytubulosine is 0.05µg/mL, giving a 50% effect when administered. The IC<sub>50</sub> value of Beta-carboline harmaline and the standard drug Paclitaxel is 34±12µM and >10µg/ml, respectively. The IC<sub>50</sub> is the inhibitory concentration required to inhibit the biological or biochemical activity.

When the drug Paclitaxel, with an IC<sub>50</sub> value of 34±12µM, is administered, it will inhibit the progression of cancer by 50%. Likewise, when Beta-carboline harmaline, with an IC<sub>50</sub> value>10µg/ml, is administered, it will inhibit the biological activity of the cell responsible for the progression of cancer. (Mangal *et al.*, 2013).

### Retrieval of the target molecule

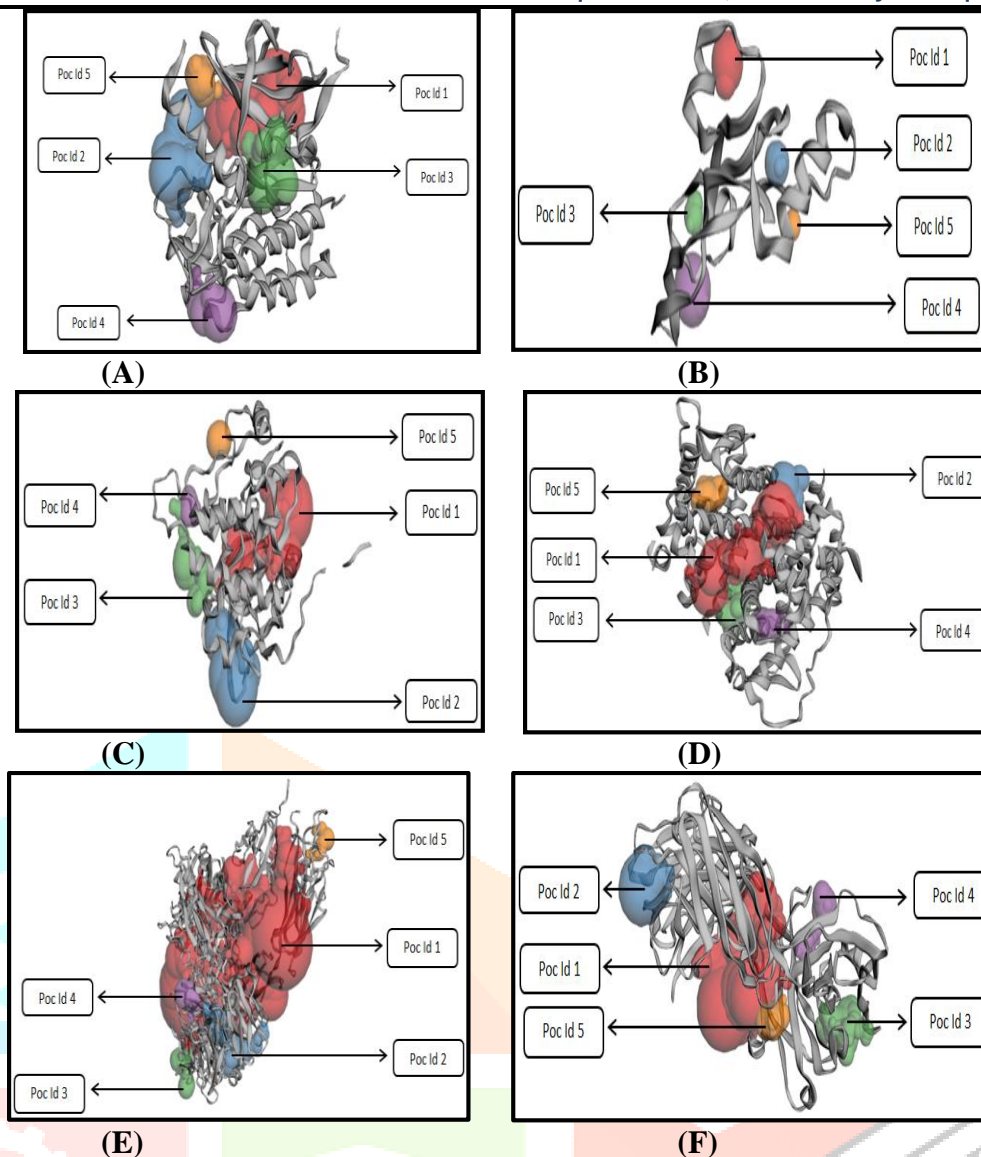
Target molecules are the receptors in the cells where the ligand binds and starts the signaling pathway. In this study, the target molecule was the protein present in the cell and is involved in the disease progression, which can be targeted by a drug to produce a therapeutic effect. For the retrieval of the target molecule, the PDB database was used (Sussman *et al.*, 1998). The target molecules used are EGFR (3VJO), TGF (1TGJ), IGFR (5FXR), Estrogen receptor (1YYE), Integrin receptor (IU8C), and Tubulin receptor (6QVE). The 3D structure of the target molecules retrieved is described in figure 2.



**Figure 2: Structure of the target molecule. [(A) EFGR, (B) TGF, (C) IFGR, (D) Estrogen receptor, (E) Integrin receptor, (F) Tubulin receptor]**

### **Prediction of binding sites of the target molecule**

The protein's binding site is the region where the ligand binds during the biochemical reaction. Many binding sites are present in a protein involved in the biochemical reaction. To predict the binding site in a protein, CASTp server was used (Tian *et al.*, 2018). Many binding sites were obtained, out of which 5 of them were selected. As it is said, 85% of the binding site having higher area and volume is involved in binding with the ligand (Binkowski, Naghibzadeh, and Liang, 2003). The binding sites of the target molecules are labelled in Figure 3.



**Figure 3: Binding site of target molecule [(A) EGFR, (B) TGF, (C) IGFR, (D) Estrogen receptor, (E) Integrin receptor, (F) Tubulin receptor]**

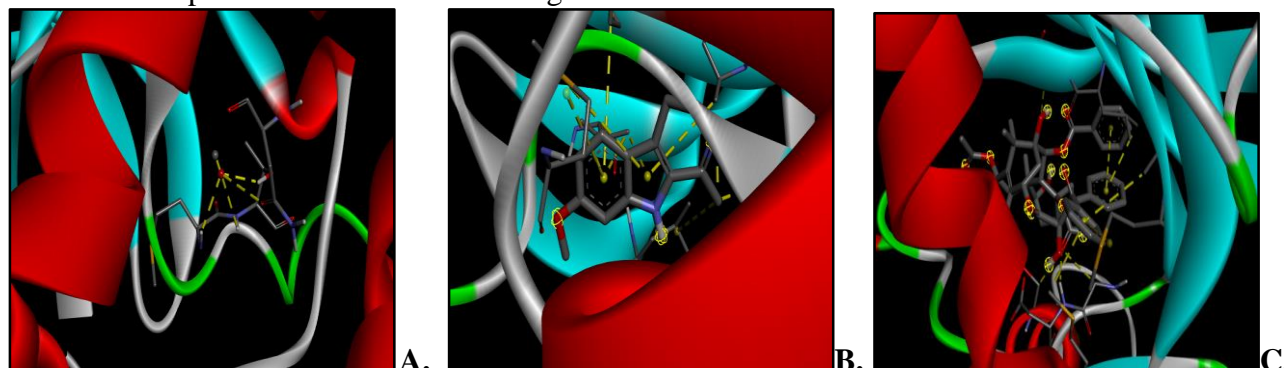
### Binding affinity study of target molecule and ligand

The binding affinity is the strength of interaction between the ligand molecule and the target molecule, which binds reversibly. The binding affinity is determined to determine how precisely a ligand is bound to its target molecule. To determine the binding affinity of the ligand and target molecule, molecular docking is performed. Molecular docking is a method used to predict how a target molecule and the ligand molecule fit together. (Schleinkofer, Wang and Wade, 2006) Normally, docking is a molecular modelling method that can be used to predict how a protein interacts with small molecules. So, to predict the binding affinity, many diverse types of molecular docking tools are used. In this study, an AutoDock tool is used for molecular docking. The binding affinity of the ligand molecule with the receptor is described in Table 2.

**Table 2: Binding affinity of the target molecule with ligand**

Name of the target molecule	Deoxytubulosine (kcal/mol)	Beta-carboline harmaline (kcal/mol)	Paclitaxel (kcal/mol)
<b>EGFR</b>	-1.6	-8.3	-6.4
<b>TGF</b>	-1.5	-5.6	-5.7
<b>IGFR</b>	-1.8	-7.7	-8.2
<b>Estrogen receptor</b>	-1.7	-6.0	-6.7
<b>Integrin receptor</b>	-1.8	-5.7	-6.7
<b>Tubulin Receptor</b>	-1.3	-5.9	-7.0

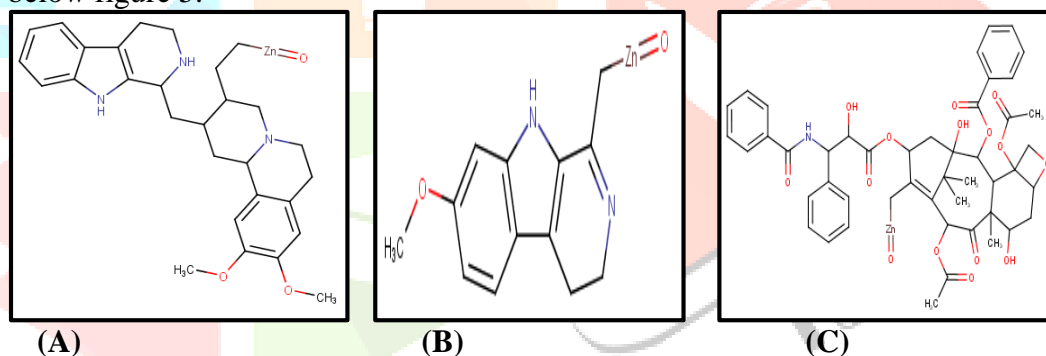
On seeing the table, it can be predicted that there was a vast difference between the binding affinity of Deoxytubulosine and drug Paclitaxel. Still, it was not identical in the binding affinity of Beta-carboline harmaline with drug Paclitaxel. Henceforth, the compound Beta-carboline harmaline can be used as lead compound to form the drug which can be further used to treat the CRC. According to the table 2, the binding affinity of the IGFR with the ligand molecules came out to be highest i.e., for Deoxytubulosine the value is -1.8kcal/mol, for beta-carboline harmaline the value is -7.7kcal/mol and for paclitaxel the value -8.2kcal/mol. So, the receptor IGFR was selected for the further use. The binding between the ligand and the IGFR receptor is described in below figure 4.



**Figure 4: Binding between IGFR and the compounds (A. IGFR with deoxytubulosine; B. IGFR with Beta-carboline harmaline; C. IGFR with Paclitaxel)**

### Modification of the compounds using bioinformatics tool

The modification of the compound was done for the enhancement of the activity. If the activity increases, the compound can be used as a lead compound to prepare the drug. In this study, the compounds were modified by adding Zinc oxide group. For the modification of the structure Molinspiration tool was used (Manoj Kumar, Renuka Swathi and Padma Sree, 2018). The insertion of the canonical smiles in the Molinspiration tool formed the structure. The structure of the modified compound with Zinc Oxide is described in below figure 5.



**Figure 5: Structures of the modified compounds. [(A) Deoxytubulosine+ZnO, (B) Beta-carboline harmaline, (C) Paclitaxel]**

Properties of the modified compounds obtained from the Molinspiration are described in the table 3.

**Table 3: Detail properties of the modified compounds**

Name of the compound	Deoxytubulosine +ZnO	Beta-carboline harmaline + ZnO	Paclitaxel +ZnO
MillogP	4.09	1.64	3.67
TPSA	66.59	54.64	238.38
natoms	36	18	64
Molecular weight	540.01	294.65	934.30
nOH	6	4	16
nOHNH	2	1	4
nrotb	7	3	16
Volume	485.54	240.22	795.67

The logP value is used to check the permeability of the drug to reach the target tissue. If the logP value is greater than 1, the drug is lipophilic. The logP value is lower than 5 as suggested in lipinski's rule. As seen in the table 3, the logP value of all the 3 compounds modified by adding ZnO is greater than 1. It means that all the compounds are lipophilic.

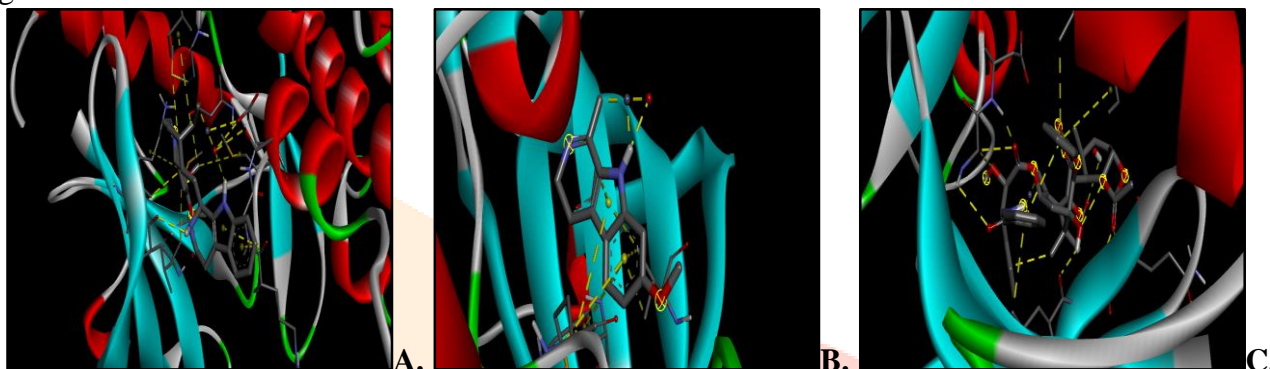
The TPSA is Molecular Polar Surface Area determined for the absorption, bioavailability, CACO2 permeability and blood-brain barrier. If TPSA is greater than 140Å, the compound is said to have poor

properties. TPSA should be lesser than 90Å for better results. nOH (hydrogen bond donor), nOHNH (hydrogen bond acceptor) should be greater than 5 and greater than 10. nrotb is for the rotatable bonds present in the compounds. This parameter is studied for the molecule flexibility and to check whether the drug can be administered orally. All the compounds are the natural compounds and so they can be excluded from the lipinski's rule (Quispe-Tintaya, 2017) If the compounds do not follow Lipinski's rule, they are also accepted for further use.

### Molecular docking of the target molecule and the modified compounds

The molecular docking was performed to determine the binding affinity and the RMSD of the target molecule and the ligand (Ma, Chan and Leung, 2011) In this study, the molecular docking was done using PyRx, and the result was visualized in the Discovery Studio.

The ligand molecule used in the molecular docking is the modified compound prepared by adding ZnO to the original compound—the receptor molecule IGFR, which showed the highest binding affinity with the original compounds. The binding between the IGFR and the compounds modified is described below in figure 6.



**Figure 6: Binding between IGFR and the modified compounds (A. IGFR with deoxytubulosine; B. IGFR with Beta-carboline harmaline; C. IGFR with Paclitaxel)**

The binding affinity between IGFR and modified Deoxytubulosine was -9.3kcal/mol, with modified Beta-carboline harmaline was -7.7kcal/mol, and with Paclitaxel was -6.5kcal/mol. Comparing Table 2, it can be said that the binding affinity has been increased when the compound is modified by adding ZnO.

### Pharmacokinetics prediction of the compounds.

The compound's pharmacokinetic properties were performed to predict absorption, distribution, metabolism, excretion, and toxicity. The ADMET describes the pharmacological activity of the compound as a drug. For the ADMET prediction pkCSM tool was used. pkCSM is the database which predicts the ADMET based on graph-based signatures (D. E. V. Pires, Blundell and Ascher, 2015). The ADMET also helps to reduce the risk of the compounds when marketed.

The absorption of the drug is referred as the way drug is being absorbed in the body when administered. Distribution refers to the movement of the drug to and from blood and tissues and the relative proportion in the blood. Metabolism of the drug is described as the biotransformation of the pharmaceutical substance so that the elimination of the substance is straightforward. Excretion of the drug is defined as elimination of the drug in the form of metabolite. There are various routes for the excretion of the drug like urine, sweat, bile and tears. Toxicity of the drug is referred as how poisonous or harmful a drug is when administered in the body.

**Table 4: Characteristics of the ADMET properties**

Properties	Characteristics	D	B	P	D1	B1	P1
Absorption	H <sub>2</sub> O solubility	-4.057	-3.123	-3.158	-3.949	-3.386	-3.08
	CACO <sub>2</sub> permeability	0.883	1.621	0.623	0.734	1.294	0.551
	Intestinal absorption	91.208	93.622	100	90.441	93.69	100
	P glycoprotein substrate	Yes	Yes	Yes	Yes	Yes	Yes
Distribution	VD <sub>ss</sub>	2.005	0.264	1.458	1.759	0.104	1.404
	Unbound fraction	0.18	0.267	0	0.196	0.253	0.013
Metabolism	CYP2D6	Yes	Yes	No	Yes	Yes	No
	CYP3A4	Yes	No	Yes	Yes	Yes	No
	CYP1A2	Yes	Yes	No	Yes	Yes	No
	CYPC19	No	No	No	Yes	No	No
	CYP2D6	No	No	No	No	No	No

	<b>CYP2C9</b>	Yes	No	No	Yes	No	No
	<b>CYP3A4</b>	No	No	Yes	No	No	Yes
<b>Excretion</b>	<b>Total clearance</b>	1.057	0.576	-0.36	2.293	1.584	-0.838
	<b>Renal OCT2 substrate</b>	Yes	Yes	No	Yes	No	No
<b>Toxicity</b>	<b>AMES</b>	No	No	No	No	No	No
	<b>Maximum tolerated dose</b>	-0.154	-0.179	0.199	-0.161	-0.16	0.244
	<b>hERG I</b>	No	No	No	No	No	No
	<b>hERG II</b>	Yes	No	Yes	Yes	No	Yes
	<b>Oral rat acute toxicity</b>	2.622	2.452	2.776	2.495	2.448	2.76
	<b>Oral rat chronic toxicity</b>	1.266	1.699	3.393	1.457	1.333	3.382
	<b>Hepatotoxicity</b>	Yes	No	Yes	No	No	Yes
	<b>T. pyriformis</b>	0.327	1.34	0.285	0.3	1.664	0.285
	<b>Minnow toxicity</b>	-0.854	0.529	2.988	-1.159	0.099	2.807

(\*D- Deoxytubulosine, B- Beta-carboline harmaline, P- Paclitaxel, D1- Deoxytubulosine with ZnO, B1- Beta-carboline harmaline with ZnO, P1- Paclitaxel with ZnO)

In ADMET properties the focus lies in the absorption, distribution, and toxicity. From the table 4, Beta-carboline harmaline and modified Beta-carboline harmaline showed better results in the absorption and distribution. It also showed that it is less toxic than the standard drug Paclitaxel. (D. E. V Pires, Blundell and Ascher, 2015).

## Conclusion

There are plant compounds that possess anticancer properties, and out of them, some are being used. This study used plant *A. salviifolium*, which contains alkaloids that are said to have anticancer properties. The alkaloids are Deoxytubulosine and Beta-carboline harmaline. The anticancer activity of the compounds was predicted using the NPACT database, and the compound Beta-carboline harmaline should have better activity than Deoxytubulosine when compared with the standard drug Paclitaxel. Then, the binding affinity study was carried out, which also showed that the Beta-carboline harmaline (-7.7 kcal/mol) has better binding activity with the receptor IGFR than Deoxytubulosine (-1.8 kcal/mol) as compared to Paclitaxel (-8.2 kcal/mol). These findings demonstrated that Beta-carboline harmaline is superior, although the ZnO group was attached to increase activity. This alteration was made since ZnO also has anticancer qualities and could boost the compounds' activity. The compound's ADMET properties also suggest that Beta-carboline harmaline, when modified with ZnO [-0.16 log (mg/kg/day)], performed better than Deoxytubulosine and the conventional medicine Paclitaxel [0.244log (mg/kg/day)] and had less toxicity. It is concluded that the molecule beta-carboline harmaline can be employed further for in vitro testing of the medicine, which has decreased toxicity and hence can create fewer side effects.

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## Author's Contribution:

Avani Shah: Experimentations, Manuscript writing-editing

Khushal Patel: Study Design, Concept, Experimentations, Manuscript writing-editing, Supervision

Pratiksha Gondkar: Validation, Manuscript editing

Digvijaysinh Rana: Study Design, Concept, Supervision, Validation

## Conflict of interest

The authors declare no conflict of interest.

## References

1. Aiello, P. *et al.* (2019) 'Medicinal plants in the prevention and treatment of colon cancer', *Oxidative Medicine and Cellular Longevity*, 2019. doi: 10.1155/2019/2075614.
2. Binkowski, T. A., Naghibzadeh, S. and Liang, J. (2003) 'CASTp: Computed Atlas of Surface Topography of proteins', *Nucleic Acids Research*, 31(13), pp. 3352–3355. doi: 10.1093/nar/gkg512.
3. Brogi, S. *et al.* (2020) 'Editorial: In silico Methods for Drug Design and Discovery', *Frontiers in Chemistry*, 8(August), pp. 1–5. doi: 10.3389/fchem.2020.00612.
4. Bundela, S., Sharma, A. and Bisen, P. S. (2015) 'Potential compounds for oral cancer treatment:



- Resveratrol, nimbolide, lovastatin, bortezomib, vorinostat, berberine, pterostilbene, deguelin, andrographolide, and colchicine', *PLoS ONE*, 10(11), pp. 1–31. doi: 10.1371/journal.pone.0141719.
5. C, P., SHASHIKUMARA, S. and T, T. (2019) 'Evaluation of Anticancer Potential of Ethanolic Extract of Alangium Salvifolium Leaves in Animal Models', *Asian Journal of Pharmaceutical and Clinical Research*, 12(2), pp. 397–400. doi: 10.22159/ajpcr.2019.v12i2.29601.
  6. Van Der Jeught, K. *et al.* (2018) 'Drug resistance and new therapies in colorectal cancer', *World Journal of Gastroenterology*, 24(34), pp. 3834–3848. doi: 10.3748/wjg.v24.i34.3834.
  7. Kim, S. *et al.* (2016) 'PubChem substance and compound databases', *Nucleic Acids Research*, 44(D1), pp. D1202–D1213. doi: 10.1093/nar/gkv951.
  8. Ma, D. L., Chan, D. S. H. and Leung, C. H. (2011) 'Molecular docking for virtual screening of natural product databases', *Chemical Science*, 2(9), pp. 1656–1665. doi: 10.1039/c1sc00152c.
  9. Mangal, M. *et al.* (2013) 'NPACT: Naturally occurring plant-based anti-cancer compound-activity-target database', *Nucleic Acids Research*, 41(D1), pp. 1124–1129. doi: 10.1093/nar/gks1047.
  10. Manoj Kumar, M., Renuka Swathi, B. and Padma Sree, G. (2018) 'Admet Predictors Are the Tools for the Enhancement of Drug Design and Development: a Systematic Review', *International Journal of Advances in Pharmacy and Biotechnology*, 4(4), pp. 6–13. doi: 10.38111/ijapb.20180404002.
  11. Mondal, A. *et al.* (2019) 'Alkaloids for cancer prevention and therapy: Current progress and future perspectives', *European Journal of Pharmacology*. Elsevier B.V., 858(November 2018), p. 172472. doi: 10.1016/j.ejphar.2019.172472.
  12. P. BAMA, M. S. (2011) 'Extraction, Identification and Characterisation of two Anti-cancer compound of Alangium Salviifolium', (April), pp. 1–224.
  13. Pires, D. E. V., Blundell, T. L. and Ascher, D. B. (2015) 'pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures', *Journal of Medicinal Chemistry*, 58(9), pp. 4066–4072. doi: 10.1021/acs.jmedchem.5b00104.
  14. Pires, D. E. V., Blundell, T. L. and Ascher, D. B. (2015) 'pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures (Theory- How to Interpret pkCSM Result)', *pkCSM*, p. 5. Available at: <http://biosig.unimelb.edu.au/pkcsm/theory>.
  15. Quispe-Tintaya, W. (2017) '乳鼠心肌提取 HHS Public Access', *Physiology & behavior*, 176(3), pp. 139–148. doi: 10.1016/j.addr.2016.05.007.BDDCS.
  16. Ratra, M. *et al.* (2012) 'Phytochemistry and pharmacology of Alangium salvifolium: A review', *Pharmacognosy Journal*, 4(2), pp. 1423–1425. Available at: [http://jpr solutions.info/newfiles/journal-file-56d51d1897bdb4.51621161.pdf%0Ahttp://linkinghub.elsevier.com/retrieve/pii/S1110093117300340%0Ahttp://dx.doi.org/10.1016/S1995-7645\(11\)60216-2%0Ahttp://phcogj.com/article/126%0Ahttp://academicjournals.org/jour](http://jpr solutions.info/newfiles/journal-file-56d51d1897bdb4.51621161.pdf%0Ahttp://linkinghub.elsevier.com/retrieve/pii/S1110093117300340%0Ahttp://dx.doi.org/10.1016/S1995-7645(11)60216-2%0Ahttp://phcogj.com/article/126%0Ahttp://academicjournals.org/jour).
  17. Schleinkofer, K., Wang, T. and Wade, R. C. (2006) 'Molecular Docking', *Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine*, 443, pp. 1149–1153. doi: 10.1007/3-540-29623-9\_3820.
  18. Shrivaya, S., Vinod, B. N. and Sunil, C. (2017) 'Pharmacological and phytochemical studies of Alangium salvifolium Wang. – A review', *Bulletin of Faculty of Pharmacy, Cairo University*. Faculty of Pharmacy, Cairo University, 55(2), pp. 217–222. doi: 10.1016/j.bfopcu.2017.07.001.
  19. Solowey, Elisha *et al.* (2014) 'Evaluating medicinal plants for anticancer activity', *Scientific World Journal*, 2014. doi: 10.1155/2014/721402.
  20. Sussman, J. L. *et al.* (1998) 'Protein Data Bank (PDB): Database of three-dimensional structural information of biological macromolecules', *Acta Crystallographica Section D: Biological Crystallography*. International Union of Crystallography, 54(6 I), pp. 1078–1084. doi: 10.1107/S09074444998009378.
  21. Tian, W. *et al.* (2018) 'CASTp 3.0: Computed atlas of surface topography of proteins', *Nucleic Acids Research*. Oxford University Press, 46(W1), pp. W363–W367. doi: 10.1093/nar/gky473.
  22. Wishart, D. S. *et al.* (2008) 'DrugBank: A knowledgebase for drugs, drug actions and drug targets', *Nucleic Acids Research*, 36(SUPPL. 1), pp. 901–906. doi: 10.1093/nar/gkm958.